

MEETING OF THE RADIOLOGICAL DEVICES PANEL

November 6, 2000

OPEN SESSION

**Conference Room 020B
Corporate Building
9200 Corporate Blvd.
Rockville, Maryland**

**Participants in the Radiological Devices Panel Meeting
November 6, 2000**

Voting Members

Brian S. Garra, M.D.
University of Vermont
Chairperson

Steven E. Harms, M.D.
University of Arkansas Medical School

Arnold W. Malcolm, M.D.
Provident St. Joseph Medical Center

Alicia Y. Toledano, Sc.D.
Brown University, Rhode Island

Nonvoting Members

Marilyn R. Peters, M.N., M.P.H.
Veterans Affairs Medical Center
Consumer Representative

Ernest L. Stern
Thomson Components and Tube Corporation
Industry Representative

Temporary Voting Members

Geoffrey S. Ibbott, Ph.D.
University of Kentucky Medical Center

Minesh Mehta, M.D.
University of Wisconsin-Madison

Temporary Non-Voting Member

Robert Ayres
Liaison, U.S. Nuclear Regulatory Commission

FDA Participants

Bernard Statland, M.D., Ph.D.
Director, Office of Device Evaluation

Daniel Schultz, M.D.
Acting Director, Division of Reproductive, Abdominal, and Radiological Devices

Robert J. Doyle
Panel Executive Secretary

Robert A. Phillips, Ph.D.
John C. Monahan
Andrew Kang, M.D.
Lakshmi Vishnuvajjala, Ph.D.

Sponsor Representatives

Alex Donald
Monica Hope, M.P.S., Ph.D.
Bruce Gray, M.D.
Val Gebski

OPEN SESSION—NOVEMBER 6, 2000

Panel Chair Brian S. Garra, M.D., opened the meeting at 10:05 a.m., noting that the voting members present constituted a quorum and asking all members to introduce themselves. He introduced **Bernard Statland, M.D., Ph.D.**, director of the Office of Device Evaluation at the Food and Drug Administration. Dr. Statland read a certification of appreciation for outgoing panel member A. Patricia Romilly-Harper, M.D., who was unable to attend the session because of bad weather, and said that a plaque of appreciation from the commissioner would be sent to her.

Robert A. Phillips, Ph.D., gave the panel an update on activities in the Radiology area. He listed five major approvals since the December 16, 1999 panel meeting: General Electric's Senographe 2000D Full Field Digital Mammographic System, McCue PLC's McCue Cubaclical Ultrasonic Bone Sonometry System, Sunlight Ultrasound Tech's Sunlight Omniscence Ultrasound Bone Sonometer, Metra Biosystems' QUS-2 Calcaneal Ultrasonometer, and Osteometer Medtech's DTU-ONE Ultrasound. Information Scanner. He noted that all supporting information for these applications is available at the FDA website.

Panel Executive Secretary Robert J. Doyle read the conflict of interest statement and noted that Steven E. Harms, M.D., and Arnold W. Malcolm, M.D., had reported interests in firms potentially affected by the day's deliberations but had been granted waivers allowing their participation. Matters unrelated to the panel discussion involving Geoffrey S. Ibbott, Ph.D., had been considered, and his full participation allowed. Mr. Doyle also read appointments to temporary voting status for Dr. Ibbott and for Minesh Mehta, M.D.

Mr. Doyle noted that the FDA seeks to encourage communication with industry through

premeetings with sponsors and through guidance documents that summarize previously requested information or knowledge amassed in certain areas. Comments from industry on these documents are always welcome. Mr. Doyle announced two tentative future panel meetings on February 5 and May 14, 2001.

OPEN PUBLIC HEARING

There were no requests to address the panel.

OPEN COMMITTEE DISCUSSION—PREMARKET APPROVAL APPLICATION P990065 FOR SIRTEX MEDICAL, LIMITED'S SIR-SPHERES

Panel Chair Dr. Garra read the charge to the panel, which was to consider a premarket approval application for SIR-Spheres, an embolic radiation therapy device.

Sponsor Presentation

Mr. Alan Donald introduced the SIR-Spheres device, which consists of radioactive microspheres of Yttrium 90 in water intended for implantation into malignant liver tumors for the purpose of selectively delivering high doses of ionizing radiation to the tumors. SIR-Spheres are delivered into the hepatic artery via either a trans-femoral catheter or a permanently implanted hepatic artery port with catheter, after which the spheres become lodged in the micro-vascular network of the tumor. Mr. Donald noted from a regulatory perspective that the FDA had approved a similar device in December 1999 from Nordium called TheraSpheres, which provided an analog application. Mr. Donald also introduced the sponsor team.

Monica Hope, M.P.S., Ph.D., described the device and its use in treating liver cancer. The device seeks to selectively place a radioactive source in intimate contact with liver tumors and to deliver

a cytocidal radiation dose to the tumors while sparing the normal liver tissue and other extra-hepatic tissues. SIR-Spheres uses a minimally invasive implantation procedure to implant a radioactive source for simultaneous treatment of all tumors, regardless of number and location in the liver. The concept is not new; this particular device uses Yttrium-90 microspheres, which are biocompatible, sterilizable and sized to allow selective lodgment and retention in tumors as well as a minimally invasive delivery. The Yttrium-90 isotope used provides a high-energy emission with minimal penetration depth and a half-life allowing a two-week delivery time. The spheres are delivered in a sealed glass vial marked with calibration time and date. Dr. Hope also described delivery of the device by port or transfemoral implantation.

Bruce Gray, M.D., presented statistics on the clinical problem of colorectal cancer and liver metastases, noting that the ability to limit and treat non-localized liver metastases would be a significant advance. While resection is the standard treatment for localized liver cancer, the vast majority of liver cancer patients have widespread, non-resectable tumors for which no treatment has previously been shown to significantly affect survival. Dr. Gray outlined alternative treatments such as cryotherapy, sclerotherapy and laser ablation, radio frequency tissue ablation, and systemic chemotherapy for colorectal liver metastases. Another technique is regional or hepatic artery chemotherapy in which ports are implanted surgically to allow direct implantation. The Cancer Research Institute of Melbourne University has been working with a technique called Selective Internal Radiation Therapy or SIRT with SIR-Spheres throughout the 1980s and 1990s to utilize the hepatic vasculature to manipulate tumor blood flow to implant through the hepatic artery a noxious substance designed to be entrapped in the tumor's vascular bed. He noted that SIR Spheres have characteristics that are ideal for remaining in the

tumor's small blood vessels and rim.

Dr. Gray summarized Phase 2 data published two months ago on 87 patients with advanced nonresectable liver cancer, in which 16 patients were implanted with SIR-Spheres alone and 71 with SIR-Spheres and hepatic artery chemotherapy (HAC). In those who received SIR-Spheres alone, there was some diminution in tumor size in $\frac{3}{4}$ of the patients and a decrease in the CEA serologic marker for cancer in 100% of the subjects. The SIR-Spheres plus HAC arm also showed a high response rate, with 86% showing a decrease in tumor size and some 75 % showing a partial or complete response, while the vast majority showed a decrease in CEA. Survival from diagnosis was significantly longer for those treated with SIR-Spheres plus HAC by a mean of 21 months.

Val Gebski outlined the pivotal Phase 3 Trial of SIR-Spheres, which was originally designed to be a randomized comparison of 95 patients suffering from advanced colorectal metastases comparing a control arm of aggressive chemotherapy to an investigational arm of a single shot of SIR-Spheres, but accrual ceased at 74 patients because of patient demand for SIRT. Trial objectives were to monitor tumor response, time to disease progression in the liver, survival, toxicity, and quality of life. Mr. Gebski defined complete and partial response, and noted that all source data for the intention to treat analysis were independently monitored, with tumor volume determined blindly by two independent evaluators. He listed the statistical methods used for response comparisons, tests for normality, test of two proportions, and time to event data, as well as assessment of quality of life. After defining survival and time to disease progression, Mr. Gebski stated that overall survival benefit of SIRT did not reach statistical significance but after 15 months patients on the SIRT arm appeared to live longer. A time-dependent Cox regression analysis showed that there is little difference between treatments up to 15

months because of patients dying of disease outside the liver, but significant survival benefit for patients on SIRT are shown for those surviving after 15 months.

Dr. Gray presented further data from the Phase 3 trial, noting that 44% of those with the device showed a complete or partial response in tumor area, compared to 18% of those with chemotherapy alone. Of those with the device, 50% showed a complete or partial response in tumor volume, compared to 24 % on chemotherapy alone. Measurements of serological markers showed a 72% response in the device arm, compared to a 47 % response rate in the control arm. At the FDA's request, results were reanalyzed with a less stringent definition of response and showed a 69% response rate for device in reducing tumor area, compared to a 32% rate on chemotherapy alone. Other parameters of efficacy such as time to disease progression, as measured by tumor area or volume, showed increased survival time in the device arm, as did CEA measurements. There was no difference in quality of life between the investigational and control arms, and most toxicity was associated with the effects of chemotherapy. There was also no difference in total number of adverse events between the two arms.

Dr. Gray added that anecdotal experience suggests that patients being treated with SIR-Spheres may occasionally be downstaged from advanced liver cancer to resectability. He cited a 1999 study of 71 patients treated with SIR-Spheres in which 89% showed a response with alpha-fetoprotein, 27% a response by CT scan, and 6% were rendered resectable. He concluded by reiterating that in the Phase 3 trial of SIR-Spheres, response rate in two-year survival increased by 13% and in three-year survival by 8%. Mean and median survival increased in the device arm, as did time to disease progression, any tumor response, and decrease in CEA.

FDA Presentation

John C. Monahan introduced the FDA review team for PMA P990065. He described the device, which consists of radioactive microspheres of Yttrium 90 in water for embolization in the microvasculature of liver tumors. He listed a number of preclinical studies designed to show the physiology of blood flow to liver cancer, the distribution of tracer microspheres, tumor blood flow as a function of tumor size, the distribution of different sized microspheres, the vasculature of micrometastases, and radiation dosimetry in normal liver tissue. Preclinical biocompatibility studies, which are particularly relevant because the microspheres lodge in vascular structures, were done on mutation, cytogenetic activity, hemocompatibility, cytotoxicity, sensitization, tissue toxicity, and systemic toxicity. Mr. Monahan concluded that the only one of these studies that produced any negative effect showed a mild dermal sensitization that did not appear to be a problem for patients but was added as a precaution in the labeling.

Andrew Kang, M.D., summarized the FDA clinical review. He noted that of the 130,000 new patients with colon cancer in the United States annually, 50,000 develop liver metastasis, with less than 30% of those being surgically resectable. Most patients have less than one year of survival. He explained the original study design, which was to achieve a median survival rate increase of 30% in SIRT patients over the chemotherapy control arm, in a randomized controlled trial of 95 patients over three years. However, the study ended with 70 patients after six years because of randomization difficulties. The trial enrolled patients with proven metastatic colon cancer in the liver with surgically unresectable tumors and no other proven metastasis. The investigation arm consisted of 36 patients treated with SIR Therapy plus hepatic arterial chemotherapy (HAC) versus a control arm of 34 patients

treated with HAC only. Primary study objectives initially included overall survival and quality of life; secondary objectives included comparison of toxicity and tumor response rates. Dr. Kang explained tumor stratification and dosimetry and noted that distribution of tumor involvement was very similar in the two arms.

Safety assessments included adverse events, radiation safety, and material safety, all of which Dr. Kang defined. Toxicity and serious adverse event results were very similar between the two arms. Radiation safety results showed no serious radiation-related toxicity events, and recent research Dr. Kang cited suggests that there is less radiation effect on normal liver tissue with SIRT than with external radiation. Material safety assessments showed that collateral circulation is not affected and that there is no permanent deterioration of liver function.

The effectiveness assessment was revised to include tumor regression rate, time to tumor progression, quality of life, and survival time. Sponsors measured tumor regression by tumor volume, tumor area, and CEA level, but the FDA does not consider CEA as reliable as tumor volume and area measures. The FDA also places higher reliance on tumor volume than area. Dr. Kang explained the sponsor definitions of partial and complete response. Tumor regression results by volume showed a significant improvement in response rates in the investigational arm. Tumor stratification and response rates by volume showed a twofold improvement in the investigational group. Median results for time to first disease progression, which the FDA sees as more reliable than mean results, also showed a significant improvement. Quality of life assessments, which were assessed by a linear analog self-assessment scale, showed equivalent results in investigational and control groups, although Dr. Kang noted that the FDA considers this assessment a part of the efficacy rather than safety assessment.

Median survival and survival by year increased in the investigational arm, but the number was too small to draw conclusions. Survival assessment after 15 months showed some improvements in the investigational arm. Dr. Kang observed that there was no increase of clinically significant Grade III-IV toxicity or serious adverse events in the SIRT arm as compared to the control. The SIRT arm showed a twofold increase of tumor regression rate and a statistically significant delay of time for tumor progression, as compared to control. However, the study failed to demonstrate a statistically significant increase in survival time.

Lakshmi Vishnuvajjala, Ph.D., gave the statistical review. She listed the original outcome measures the sponsors proposed (overall survival, quality of life, tumor response rate, and treatment complications), noting that the trial was sized to detect a 30% difference in overall survival. The device group did survive, but so did the control group, so statistical significance was not reached. Patients were stratified into three groups based on tumor volume, and the trial design used blocked randomization to achieve an analysis based on intent-to-treat. However, the trial was stopped after entering 74 patients (four of whom were deemed ineligible) over six years because of difficulty randomizing to the control arm, given the favorable results of SIRT from other studies and patient refusal to be randomized to control.

The device group showed an improvement in median survival as compared to control, but the difference was not statistically significant. Survival data stratified by tumor volume size showed similar results favoring the device group but not at a statistically significant level. Survival data at less than 15 months showed roughly similar numbers of patients dying from progression of liver metastases and disseminated cancer; survival data at 15 months or more showed fewer patients dying from progression

of liver metastases in the device arm than in control, but more from disseminated cancer. Tumor regression as indicated by volume showed a statistically significant difference favoring the device arm, as did time to first progressive disease in the liver by tumor volume. The number of serious adverse events during the protocol was similar for the two groups. Self-assessment of quality of life, based on a visual analog scale, showed similar results for the two groups.

Dr. Vishnuvajjala concluded that the study results did not bear out the expected improvement in survival: although survival for the SIRT arm was better, the difference was not statistically significant and therefore the primary endpoint was not achieved. Study objectives were revised to include tumor response rate, time to disease progression in the liver, overall survival, toxicity of the two treatment regimens, and quality of life. Of these, only the first two showed SIRT to be significantly better: time to disease progression and tumor regression as measured by volume and area. Complications and quality of life measures were similar.

At this point the Open Session was adjourned for an hour for lunch, during which the Closed Session was held.

Panel Discussion

Arnold Malcolm, M.D., lead discussant, asked for general questions from the panel. These questions dealt with clarification on reductions in volume versus area measurements, radiation safety precautions, leaching of device over time, reflux and multiple dosage, and quality assurance and training procedures. There was also considerable discussion on whether approval was sought for syringe injection or an infusion set. The FDA clarified that the administration set would be a part of the approval, but the actual choice of administration is left to the physician's discretion. It was noted that the

radiation dose a physician would be exposed to should be calculated and put in the labeling. Dr.

Malcolm then read the FDA questions for panel discussion.

FDA Questions to the Panel

- 1) Please discuss the PMA data as they pertain to providing the valid scientific evidence needed to conclude that SIR-Spheres are safe and effective for the treatment of metastatic colorectal tumors in the liver.*

The panel concluded from the data presented that the device can be used safely despite the small numbers provided in the study. It expressed concerns that to ensure safety, certain criteria must be met, including the use of the device with experienced users trained in qualified centers, the use of scans to prevent overdose, and the use of vasoconstrictors during administration of the treatment. There were statistical questions about data evaluation, given the variety of administration methods and the small numbers of patients, and the panel was divided about the significance of the data presented. Some members expressed concerns about the efficacy endpoints and data, but others found the data meaningful for patients looking for small changes and small increases in survival time. The panel agreed that the device does appear to help patients and leads some to resection or curability and to increased time of disease progression for some patients. The panel thought that although there was not a significant change in the quality of life for patients, their lives were not worsened and might in fact be bettered.

- 1b) Are there data to support the use of SIR-Spheres for the treatment of **all** (primary and secondary) malignant liver tumors, not just colorectal metastases?*

The panel agreed that there are such data, but they have not been submitted to the panel. The data presented are primarily for colorectal metastases.

2) *Is the labeling of the device, including the indications for use, appropriate, given the data provided in the PMA application? Please comment on indications, contraindication, warnings, and precautions.*

The panel reiterated that use of vasoconstrictors and performance of a study or scan to prevent overdose should be discussed in the labeling. Decisions on use of the device with specific types of patients should be a clinical decision, as should handling of patients with ascites. The lack of dosimetry information in the labeling should be remedied, as should the lack of information on clinician exposure in handling the device and on radiation protection and exposure rates. The FDA should provide input to sponsors on handling issues of potential toxicities and alternative treatments in the patient information.

3) *If the PMA is approved, should the sponsor be required to conduct postapproval studies to address any outstanding safety issues or further evaluate effectiveness based on improved survival and/or quality of life?*

There was some discussion about a postapproval study using new agents of systemic chemotherapy. Such a postapproval observational study could monitor training, use of delivery system, endpoints, and symptoms. Others argued for an observational study to track patients for safety only on the grounds that this is a palliative procedure that provides a large advantage in the risk/benefit ratio for patients who have few other options.

4) *Is there a need for mandatory training for users of the device?*

The panel agreed that mandatory training in a team setting should be specified in the device labeling.

Open Public Hearing

There were no requests to address the panel.

FDA Comments

FDA representatives had no additional remarks.

Sponsor Comments

Sponsor representatives thanked the panel and said that the members' comments had been noted and were most helpful.

Panel Recommendations and Vote

Panel Chairperson Dr. Garra read the voting instructions. A motion was made and seconded to recommend the PMA as approvable with conditions. The following conditions were proposed.

- 1) Sponsors should

Provide patient dosimetry information in the labeling.

Provide radiation protection information in the labeling.

Specify mandatory training for users.

Improve patient labeling information.

This condition carried.

- 2) The indication for use of the device should be for treatment of metastatic colorectal cancer. If the FDA receives other information on primary or secondary cancer treatment, they should move aggressively to pursue such information.

This condition carried.

- 3) A postapproval study (an observational study would be acceptable) of safety and

effectiveness should be designed with the FDA, to include the use of new systemic chemotherapy agents.

This motion carried.

Comments about NRC regulations prohibiting the unknowing use of the device with pregnant women were clarified to indicate that the device could be used with pregnant women at the discretion of clinician and patient.

The motion to recommend the PMA as approvable subject to the above conditions was carried unanimously.

Panel Chairperson Dr. Garra thanked the panel, lead discussant Dr. Malcolm, and all participants in the meeting and adjourned the Open Session at 3:30 p.m.

I certify that I attended the Open Session of the Radiological Devices Panel Meeting on December 16, 1999, and that this summary accurately reflects what transpired.

Robert J. Doyle
Executive Secretary

I approve the minutes of the meeting as recorded in this summary.

Dr. Brian S. Garra
Panel Chairperson

Summary minutes prepared by Aileen M. Moodie
9821 Hollow Glen Pl.
Silver Spring, MD 20910
301-587-9722